One Year Post Exclusivity Adverse Event Review: Nelfinavir Mesylate

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Background Drug Information

- **Drug:** Viracept® (nelfinavir mesylate)
- **Therapeutic Category:** HIV protease inhibitor
- **Sponsor:** Pfizer, Inc.
- **Indication:** Treatment of HIV infection in patients ≥ 2 years
- **Original Market Approval:** March 14, 1997
- **Pediatric Exclusivity Granted:** September 4, 2003

Drug Use Trends in Outpatient Settings: Nelfinavir

- Viracept® accounted for roughly 16.4% of the 1.9 million prescriptions dispensed for the HIV protease inhibitor class in the U.S. from September 2003 to August 2004.[1]
- Dispensed prescriptions for Viracept® decreased roughly 22% from approximately 398,000 (Sep 2002 - Aug 2003) to approximately 312,000 (Sep 2003 - Aug 2004).[1]
- Pediatricians were responsible for roughly 3% (~7,000 prescriptions) of Viracept® dispensed in the U.S. between September 2003 and August 2004.[1]

[1]IMS Health, National Prescription Audit *Plus*™, Moving Annual Totals Sep 2001 –Aug 2004, Extracted Oct 2004

Pediatric Exclusivity Studies: Nelfinavir

- 5 trials in >400 HIV infected pediatric patients from birth to 17 years of age examining pharmacokinetic (PK), safety and activity of nelfinavir mesylate
  - Highly variable drug exposure remains a significant problem.
    - Considered secondary to difficulties maintaining adherence and adequate food intake in this population
    - Drug must be taken with food to ensure proper absorption.
  - Response rates in children <2 years of age appeared to be poorer than in patients ≥2 years of age in some studies.
  - Revised dosing recommendations for pediatric patients ≥2 years; not recommended for patients <2 years

Labeling Changes Resulting from Exclusivity Studies

- Inclusion of PK data for pediatric patients one week to 13 years of age demonstrating a variable drug exposure
- For children ≥2 years, dosing changed from 20-30 mg/kg TID to either 25-35 mg/kg TID or 45-55 mg/kg BID
  - Modified dosing chart added to the label
- Expanded the pediatric safety database from 38 patients to approximately 400 and listed most common pediatric adverse events

Relevant Safety Labeling

- Pediatric- Most commonly reported treatment-emergent adverse events attributable to nelfinavir mesylate:
  - Diarrhea, leukopenia/neutropenia, rash, anorexia and abdominal pain
    - Diarrhea, regardless of assigned relationship to study drug, was reported in 39% to 47% of pediatric patients receiving nelfinavir mesylate in 2 of the larger pediatric treatment trials.
    - Leukopenia/neutropenia was the laboratory abnormality most commonly reported as a significant event across the pediatric studies.

Adverse Event Reports since Market Approval: Nelfinavir 03/14/97 – 10/04/04

- Total number of reports, all ages†:
  - 3,344 reports (1,319 US)
    - 3,207 serious (1,258 US)
      - 417 deaths (205 US)
- Pediatric reports*:
  - 377 reports (149 US)
    - 374 serious (146 US)
      - 19 deaths (8 US)

†Includes reports with unknown age

*Counts may include duplicate reports

Adverse Event Reports during the One-Year Post-Exclusivity Period: Nelfinavir 09/04/03 – 10/04/04

- Total number of reports, all ages[†*]:
  - 269 reports (70 US)
    - 264 serious (67 US)
      - 33 deaths (4 US)
- Pediatric reports[*]:
  - 30 reports (9 US) (27 unduplicated reports)
    - 30 serious (9 US)
      - 2 deaths (0 US)

[†]Includes reports with unknown age

[*]Counts may include duplicate reports

Most Commonly Reported Adult Adverse Events during the One-Year Post-Exclusivity Period

- Diarrhea
- Vomiting
- Nausea
- Aspartate aminotransferase increased
- Lactic acidosis
- Anorexia
- Complication of maternal exposure to therapeutic drugs
- Pyrexia
- Alanine aminotransferase increased
- Asthenia

Includes AEs from duplicate reports Underlined events = Unlabeled events

Types of Pediatric Nelfinavir Exposure in FDA AERS Database

- **Direct: Treatment of HIV-infected pediatric patients**
  - Used in combination with other anti-retroviral agents for HIV treatment, so difficult to assign causality to reported adverse events
- **Indirect: Used during pregnancy by HIV+ mothers for maternal health and prevention of perinatal HIV**
  - Exposed infants may or may not be HIV infected
  - Possible association of combination antiretroviral (ARV) therapy and premature delivery
  - Newborns receive ARV therapy postpartum, which may complicate interpretation of adverse events associated with in utero exposure.

Pediatric Adverse Events from Direct Exposure during the One-Year Post-Exclusivity Period (n=3)

Arthritis
Attention Deficit Hyperactitivity Disorder
Bronchiolitis
Bronchiolitis obliterans
Central venous catheterization
Liver function tests abnormal
Muscular weakness
Prematurity
Psychomotor hyperactivity
Renal Tubular Acidosis
Respiratory Distress

Underlined events = Unlabeled events

Pediatric Death in Directly Exposed Patient (n=1)

- 60 week old HIV+ ex-30 week preemie
- Hospitalized with suspicion of arthritis, central line placement, experienced bronchiolitis and expired while participating in a stavudine, didanosine and nelfinavir open-label study
- Hospitalized twice for central venous catheter placement and suspicion of arthritis and also experienced two episodes of bronchiolitis
- Died secondary to respiratory distress due to bronchiolitis obliterans

Pediatric Adverse Events from In Utero Exposure during the One-Year Post-Exclusivity Period: (n=24)

- Most commonly reported AEs:
  - Prematurity
  - Birth by Cesarean-section
  - Neonatal disorder
  - Blood lactic acid increased
  - Blood lactate dehydrogenase increased
  - Gastroesophageal Reflux Disease
  - Hypertriglyceridemia
  - Patent ductus arteriosus
- One pediatric death

Sudden Death of a Neonate with In Utero Exposure to Nelfinavir (n=1)

- Term infant born to a mother who discovered her HIV+ status in third trimester. Mother started zidovudine +lamivudine & nelfinavir two weeks prior to delivery
- Delivered by C-section with apgar of 10
- Infant received two doses of zidovudine post-partum
- Found dead at 20 hours of life
- Radiographic studies, CSF cultures and electrolytes labs were normal. HIV PCR of blood was negative. Blood lactate was slightly elevated and anemia was also noted.
- Autopsy was consistent with asphyxia.
- Relationship to drug exposure unclear

Summary: Nelfinavir

- No consistent safety signal identified in the three reported pediatric adverse event cases
- Prematurity was the most common adverse event observed in infants with in utero exposure and has been reportedly associated with combination anti-retroviral therapy during pregnancy.
- This completes the one-year post-exclusivity AE monitoring as mandated by BPCA.
- FDA recommends routine monitoring of AEs for this drug in all populations.
- Does the Advisory Committee concur?

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